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(32) Priority Date: 30 September 1987 (30.09.87)

(33) Priority Country: US

(71) Applicant: THE UNIVERSITY OF TENNESSEE RESEARCH CORPORATION [US/US]; Suite 415, Communications Building, Knoxville, TN 37996 (US).

(72) Inventors: KENNEDY, Thomas, P. ; 1624 Clanlo Drive, Memphis, TN 38104 (US). KABALKA, George, W. ; 7124 Cresthill Drive, Knoxville, TN 37919 (US).

(74) Agents: HODGES, Paul, E. et al.; Luedeka, Hodges & Neely, 1030 First American Center, Knoxville, TN 37902 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

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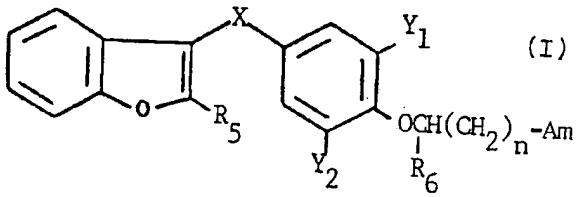
(54) Title: CERTAIN 3-SUBSTITUTED 2-ALKYL BENZOFURAN DERIVATIVES



(I)

(57) Abstract

The disclosure relates to compounds of formula (I) and pharmaceutically acceptable addition salts thereof wherein X represents a single, direct bond or a substituted or unsubstituted alkylene chain containing 1 to 4 carbon atoms, wherein R_5 is a lower alkyl group, wherein R_6 is either hydrogen or methyl, wherein Am is selected from the class consisting of amino, lower mono and dialkylamino, piperidino, piperazino, N-lower alkyl piperazino, pyrrolidino, and morpholino groups wherein Y_1 and Y_2 are identical and are hydrogen, a halogen, methyl or ethyl and n is an integer in the range of 1-5. They are useful in treating arrhythmic conditions and conditions for which treatment with a vasodilator is indicated.

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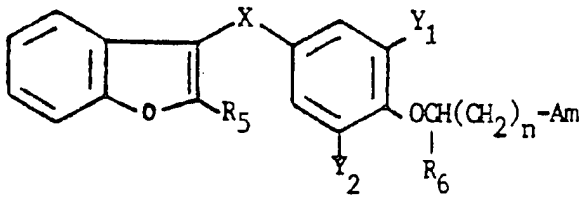
AMENDED CLAIMS
[received by the International Bureau on 30 March 1989 (30.03.89);
original claim 1 amended; other claims unchanged (1 page)]

Claim 1. A compound of the formula:



and pharmaceutically acceptable addition salts thereof wherein X represents a single, direct bond or a substituted or unsubstituted alkylene chain containing 1 to 4 carbon atoms where such substituents are one or more members selected from the group consisting of branched or straight-chain alkyl, cycloalkyl, aryl, alkoxy and the formula $-O-\overset{O}{\overset{\|}{C}}-R_4$, with R_4 being hydrogen or lower alkyl, wherein R_5 is a lower alkyl group, wherein R_6 is either hydrogen or methyl, wherein Am is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, piperazino, N-lower aklyl piperazino, pyrrolidino, and morpholino groups, wherein Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen, halogen, methyl and ethyl and n is an integer in the range of 1-5.

2. A compound as set forth in Claim 1 wherein X represents an alkylene chain having the formula $-\overset{R_1}{\overset{|}{C}}-\overset{}{\underset{R_2}{|}}$ wherein R_1 and R_2 are each selected from the class consisting of hydrogen, a group having the formula $-OR_3$ with R_3 being a lower alkyl group, and a group having the formula $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group, R_4 is butyl, R_5 is hydrogen, Am is selected from the class consisting of amino and lower mono and dialkylamino and Y_1 and Y_2 are identical and are selected from the class consisting of

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Published

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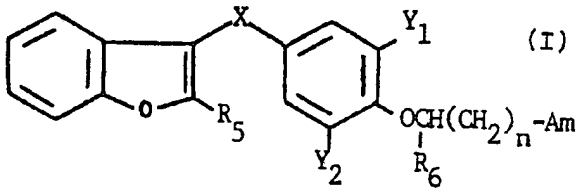
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CERTAIN 3-SUBSTITUTED 2-ALKYL BENZOFURAN DERIVATIVES



(57) Abstract

The disclosure relates to compounds of formula (I) and pharmaceutically acceptable addition salts thereof wherein X represents a single, direct bond or a substituted or unsubstituted alkylene chain containing 1 to 4 carbon atoms, wherein R_5 is a lower alkyl group, wherein R_6 is either hydrogen or methyl, wherein Am is selected from the class consisting of amino, lower mono and dialkylamino, piperidino, piperazino, N-lower alkyl piperazino, pyrrolidino, and morpholino groups wherein Y_1 and Y_2 are identical and are hydrogen, a halogen, methyl or ethyl and n is an integer in the range of 1-5. They are useful in treating arrhythmic conditions and conditions for which treatment with a vasodilator is indicated.

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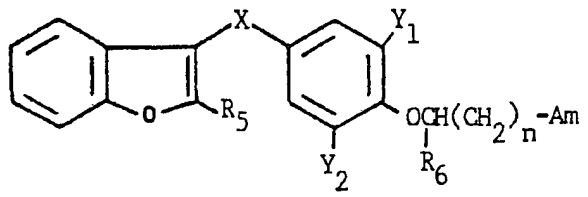
CERTAIN 3-SUBSTITUTED 2-ALKYL BENZOFURAN DERIVATIVES

The invention relates to compounds having pharmacological activity and more particularly relates to novel pharmacologically active 3-substituted 2-alkyl benzofuran derivatives, and methods for their preparation.

Compounds in accordance with the invention are represented by the general formula:



I

and pharmaceutically acceptable addition salts thereof wherein X represents a single, direct bond or a substituted or unsubstituted alkylene chain containing 1 to 4 carbon atoms, wherein R_5 is a lower alkyl group, wherein R_6 is either hydrogen or methyl, wherein Am is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, piperizino, N-lower alkyl piperizino, pyrrolidino, and morpholino groups, wherein Y_1 and Y_2 are identical and are hydrogen, halogen, methyl or ethyl, and n is an integer in the range of 1-5.

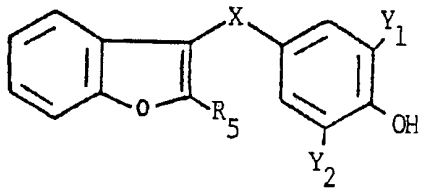
The term "unsubstituted or substituted alkylene chain containing 1 to 4 carbon atoms" is intended, unless further defined, to designate a saturated aliphatic hydrocarbon chain of between 1 and 4 carbon atoms with or without one or more substituents. Substituents are limited to those which do not diminish the pharmacological activity of the compounds below a useful level and include branched or straight-chain alkyl or cycloalkyl groups, aryl groups,

alkoxy groups, and ester substituents. "Lower alkyl" is intended to designate straight-chain, branched, or cyclic saturated aliphatic hydrocarbon groups containing 1-6 carbon atoms. "Lower mono and dialkylamino" refers to amino groups with one or two straight-chain, branched or cyclic saturated aliphatic hydrocarbon groups containing 1-6 carbon atoms. When two groups are present, they may be the same or different. Examples are methylamino, dimethylamino, ethylamino, diethylamino, n-propylamino, isopropylamino, and the like. Halogen, unless further defined, is intended to refer to fluorine, chlorine, bromine, and iodine.

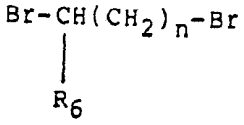
Compounds in accordance with the invention are useful as vasodilators and as antiarrythmic agents. Preferred for this purpose are compounds of Formula I above wherein X represents the Formula $-\overset{R_1}{\underset{R_2}{C}}-$ above wherein R_1 and/or R_2 are hydrogen, lower alkyl groups, groups with the Formula $-OR_3$ with R_3 being a lower alkyl group, or groups with the Formula $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group, R_5 is a lower alkyl group containing 1-4 carbon atoms, R_6 is hydrogen, Am is as defined above for Formula I, Y_1 and Y_2 are identical and are hydrogen, bromine, iodine, or methyl, and n is in the range of 1-3. Particularly preferred are compounds wherein X is $-\overset{R_1}{\underset{R_2}{C}}-$ wherein R_2 is hydrogen and R_1 is hydrogen, or $-OR_3$ with R_3 being a lower alkyl group, or R_1 is $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group, R_5 is butyl, R_6 is hydrogen, Am is amino or lower mono and dialkyl amino, Y_1 and Y_2 are identical and are hydrogen, bromine, iodine, or methyl and n is an integer in the range of 1-3. Most preferably, X is $-\overset{R_1}{\underset{R_2}{C}}-$ wherein R_2 is hydrogen and

R_1 is hydrogen or $-OR_3$ with R_3 being a lower alkyl group containing between 1 and 4 carbon atoms, or R_1 is $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group containing 1 to 4 carbon atoms, R_5 is n-butyl, R_6 is hydrogen, Am is amino, ethylamino or diethylamino, Y_1 and Y_2 are either both hydrogen, both iodine, or both methyl, and n is 1. Of the most preferred compounds, compounds where R_1 and R_2 are both hydrogen are particularly desirable.

Compounds of Formula I in which R_6 is hydrogen are prepared by first condensing an alkali metal salt of a compound represented by Formula II below in which X, R_5, Y_1 and Y_2 have the same meanings as in Formula I with a dibromoalkane represented by Formula III in which R_6 is hydrogen and n is 1-5 in an inert organic medium such as dimethyl formamide.

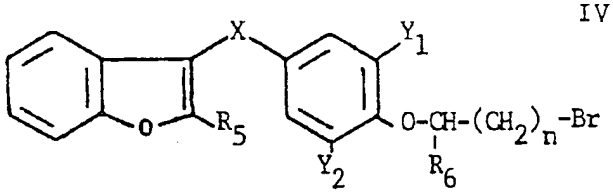


II



III

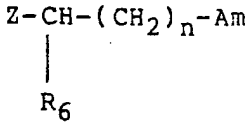
The resulting bromoalkoxy-substituted compounds of Formula IV are condensed with an amine of the Formula V in which Am has the same meaning as in Formula I in an inert solvent such as benzene to produce the Formula I compounds.



IV

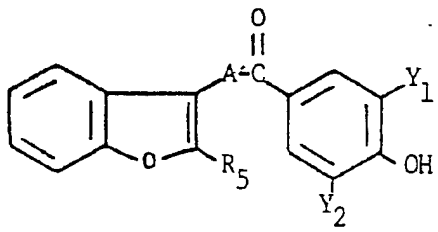
V

Alternately, when Am does not represent a secondary amine and R_6 is either hydrogen or methyl, an alkali metal salt of a compound of Formula II can be condensed with an amine represented by Formula VI in which Z is a halogen atom to produce of Formula I compounds.



VI

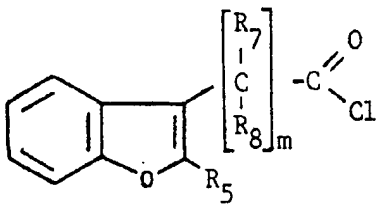
The compounds represented by Formula II can be synthesized by a number of reaction routes. As will become more apparent hereinafter, many of such compounds can be prepared by reduction of or reduction and subsequent reaction of a ketone intermediate represented by Formula VII wherein A is a single direct bond or a substituted or unsubstituted alkalene chain containing 1-3 carbon atoms in the chain and R_5, Y_1, and Y_2 are as defined in Formula I.



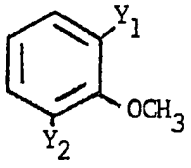
VII

When A is a single, direct bond, Formula VII ketones are known intermediates and are disclosed in U.S. Patent Nos. 3,248,401 and 3,920,707, which are incorporated herein by reference.

When A represents a substituted or unsubstituted alkalene chain containing 0-3 carbon atoms, the ketone intermediates represented by Formula VII can be prepared by Friedel-Crafts acylation of a 2, 6-substituted anisole of Formula IX with an acid chloride of Formula VIII wherein m represents an integer of 0-3 and R_7 and R_8 represent the same entities as R_1 and R_2 or precursors thereof followed by demethylation of the anisole with pyridine hydrochloride.



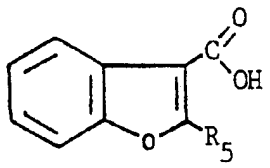
VIII



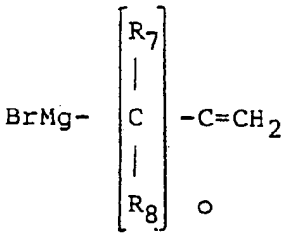
IX

The acid chlorides of Formula VIII can be prepared from 3-carboxy-2-alkyl benzofurans of the Formula X by reaction with an alkene Grignard reagent of Formula XI wherein o is 0-2 and R_7 and R_8 are defined as in Formula VIII in the presence of

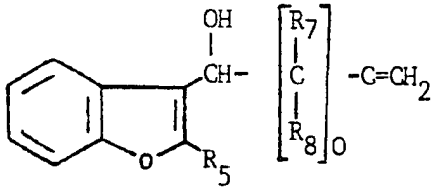
$CdCl_2$ to result in the formation of the secondary alcohols of Formula XII.



X

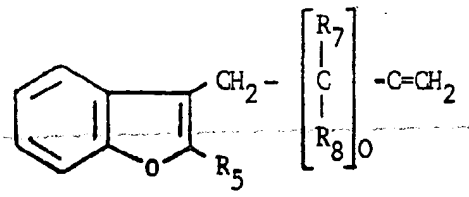


XI

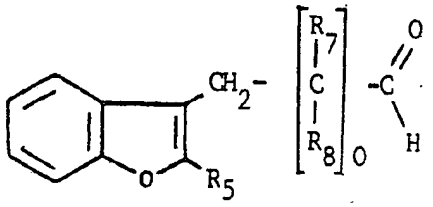


XII

Formula XII alcohols can be dehydrated to the corresponding alkenes of Formula XIII below by reaction with sulfonyl chloride in pyridine followed by reaction with lithium triethyl borohydride. Formula XIII alkene substituted benzofuran compounds are converted to acid chlorides of Formula VIII by ozination in the presence of zinc and oxidation of the resulting aldehyde of Formula XIV to the carboxylic acid employing potassium permanganate (cold) followed by reaction with sulfonyl chloride.

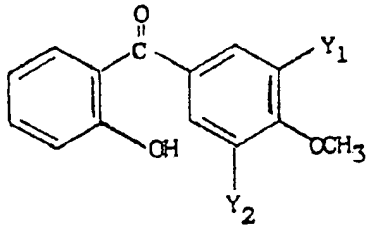


XIII

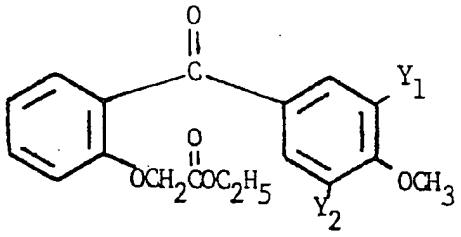


XIV

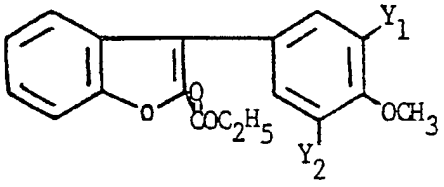
When X is a single direct bond, compounds of Formula I are prepared by first reacting a compound of Formula XV with Y_1 and Y_2 as defined in Formula I with ethyl bromoacetate in acetone in the presence of K_2CO_3 to form a compound of Formula XVI. Formula XVI compounds are converted to the compounds of Formula XVII by Perkin condensation in the presence of acetic anhydride and sodium acetate followed by the conversion of the ester group to R_5 groups. Demethylation of the substituted anisole moiety yields compounds of Formula II wherein X is a single, direct bond which can be employed as previously discussed to prepare Formula I compounds.



XV



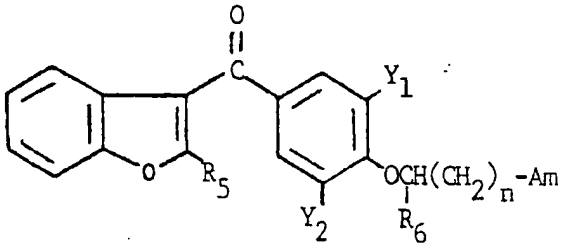
XVI



XVII

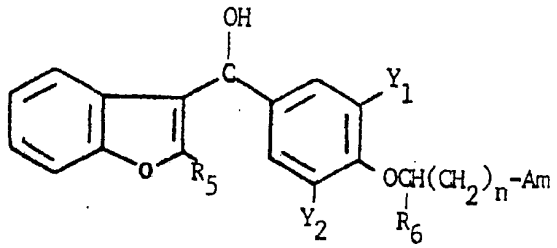
Compounds of Formula XV can be prepared by Friedel-Crafts acylation of the substituted anisoles of Formula IX with salicyloyl chloride.

The particularly preferred compounds of Formula I described above wherein X is $-\overset{R_1}{\underset{R_2}{C}}-$ and R_2 is hydrogen and R_2 is hydrogen or $-OR_3$ with R_3 being a lower alkyl group or $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group are advantageously prepared by way of an alcohol intermediate which is produced by reducing a ketone of the formula:



XVIII

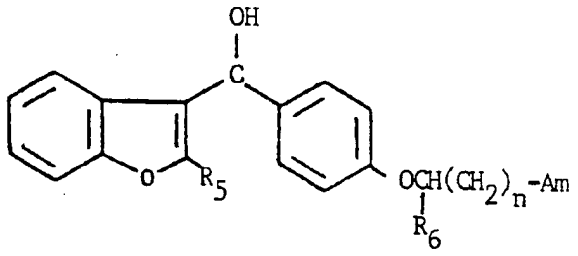
with R_4, R_5, R_6, Y_1 and Y_2, and n as defined for Formula I. Formula XVII ketones are known and procedures for their synthesis are described in U.S. Patent Nos. 3,248,401 and 3,920,707, the disclosures of which are incorporated herein by reference. To produce compounds according to Formula I wherein Y_1 and Y_2 are identical halogens, reduction of the compounds of Formula XVIII with Y_1 and Y_2 being halogens is performed under conditions which reduce the ketone group to the alcohol without otherwise affecting the molecule. A reducing system employing sodium borohydride in a tetrahydrofuran-methanol mixture (10:1 v/v) at approximately 0°C produces high yields of the alcohol represented by Formula XIX:



XIX

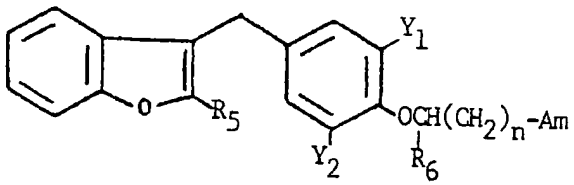
To prepare compounds of the invention wherein Y_1 and Y_2 are both hydrogen, both methyl, or both ethyl, the ketones of the Formula XIV wherein Y_1 and Y_2 are both hydrogen, both methyl or both ethyl are similarly reduced to produce the alcohol intermediate shown in Formula XX. Alternately, to produce the compounds where Y_1 and Y_2 are both hydrogen, reduction of Formula XVIII compounds wherein Y_1 and Y_2 are both halogens can be performed employing a reduction system which reduces the ketone group to the alcohol while also dehalogenating the benzene ring to produce Formula XX alcohols. Sodium borohydride in methanol in the presence of a $PdCl_2$ catalyst at 20°C is a preferred reduction

system to achieve both reduction and dehalogenation.

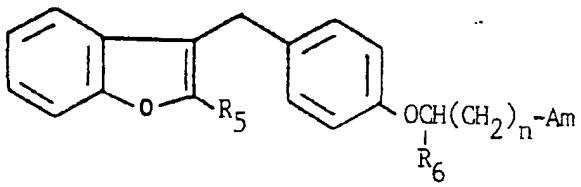


XX

Compounds of Formula I wherein X is $-\overset{R_1}{\underset{R_2}{C}}-$ and R_1 (and R_2) is hydrogen are produced from the intermediates of Formulas XIX and XX by further reduction at the alcohol group. Compounds of Formula XXI (Y_1 and Y_2 are both halogens, methyl or ethyl) or XXII (Y_1 and Y_2 are both hydrogen), when reacted in a suitable solvent at 0°C with sodium borohydride in trifluoroacetic acid produce compounds of Formulas XXI and XXII, respectively.

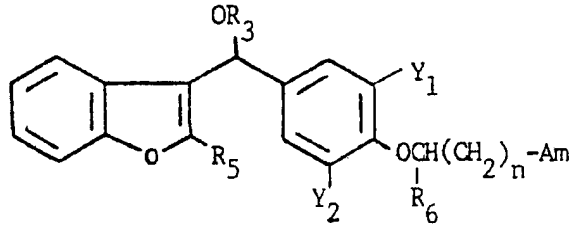


XXI

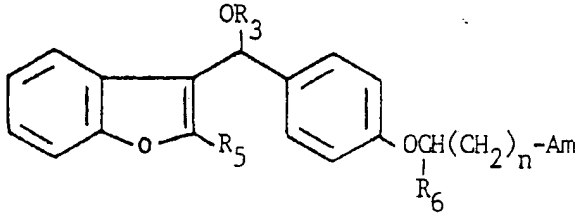


XXII

The alcohols of Formulas XIX and XX are also employed as intermediates to produce compounds wherein X is $\begin{matrix} R_1 \\ | \\ C \\ | \\ R_2 \end{matrix}$ and R_2 is hydrogen and R_1 is $-OR_3$ with R_3 being a lower alkyl group. A Williamson synthesis whereby the alcohols or Formula XIX or XVII are converted to the corresponding alkoxide and reacted with an alkyl halide of the Formula R_3X is used to produce the ethers represented by Formulas XXIII (Y_1 and Y_2 are both halogens, methyl or ethyl) and XXIV (Y_1 and Y_2 are both hydrogen).

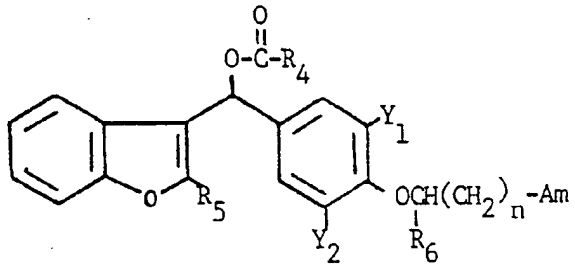


XXIII

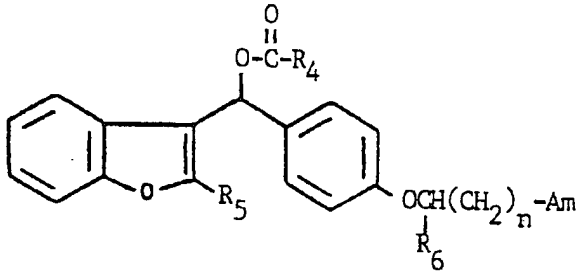


XXIV

To produce the compounds of Formula I wherein X is $-\overset{R_1}{\underset{R_2}{C}}-$ and R_1 is $-O-\overset{O}{\overset{\|}{C}}-R_4$ (R_2 is hydrogen), the alcohols of Formulas XIX and XX are esterified. Acyl halides of the formula $R_4-\overset{O}{\overset{\|}{C}}-X$ can be reacted with the alcohols of Formulas XIX or XX, respectively, preferably in the presence of a solvent capable of acting as an acid scavenger, e.g., pyridine, to produce compounds of Formulas XXV (halogenated) (Y_1 and Y_2 are both halogen, methyl or ethyl) or XXVI (Y_1 and Y_2 are both hydrogen), respectively:



XXV



XXVI

The compounds of Formula I react to form acid addition salts with pharmaceutically acceptable acids, for example, with inorganic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and with

organic acids such as acetic acid, tartaric acid, maleic acid, citric acid and toluenesulfonic acid.

The compounds of the Formula I above and the salts thereof are useful in treating arrhythmic conditions and conditions for which treatment with a vasodilator is indicated. The novel pharmaceutically active agents provided by the present invention can be administered in pharmaceutical dosage forms, internally, for example, parenterally or enterally with dosage adjusted to fit the exigencies of the therapeutic situation. The pharmaceutical dosage forms are prepared by incorporating the active ingredient in conventional liquid or solid vehicles to thereby provide emulsions, suspensions, tablets, capsules, powders and the like according to acceptable pharmaceutical practices. A wide variety of carriers or diluents as well as emulsifying agents, dispersing agents and other pharmaceutically acceptable adjuvants can be incorporated in the pharmaceutical dosage forms.

The following examples are offered to illustrate the invention and are not intended to be limiting.

EXAMPLE I

Preparation of (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methanol.

One 1 mmole (645 mg) of the ketone (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl - methanone is dissolved in 30 ml of THF:MeOH (10:1 v/v). Sodium borohydride (1.2 mmole, 45.42 mg) is added to the solution and the mixture is stirred and maintained at a temperature of 0°C until the starting material is consumed (15 minutes). Excess borohydride is destroyed by the dropwise addition of water (0.5 ml). Volatile components are removed under reduced pressure (roto-evaporator). Water is added to the residue (10 ml) followed by the addition of methylene chloride (10 ml). The methylene chloride layer is separated from the aqueous phase and is dried over anydrous sodium sulfate. The methylene chloride solvent is removed

under reduced pressure and the product is purified by column chromatography (silica gel support using methylene chloride) and is recovered by reduced pressure evaporation of the methylene chloride. The yield of the product, m.p. 106-107°C, is >50% of theoretical. (The m.p. of the hydrochloride salt is 143-145°C.)

EXAMPLE II

Preparation of (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-phenyl methanol.

One mmole (645 mg) of the ketone, (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methanone is dissolved in 10 ml of methanol. Palladium dichloride (2 mmole, 354 mg) is added and the mixture is agitated to suspend the palladium dichloride. The temperature of the mixture is adjusted to 20°C. Sodium borohydride (10 mmole, 379 mg) is added and stirring is continued until reaction is complete (1 hour). The palladium dichloride is removed by filtration and water is added to the filtrate. An ether extraction is performed and the product is removed from the ether phase by evaporation under reduced pressure. The produce is purified by chromatography (silica gel using methylene chloride) and results in >50% yield of the product, m.p. 203°C (decomposes).

EXAMPLE III

Preparation of (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methane.

One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in methylene chloride (5 ml). Sodium borohydride (38 mg, 10 mmole) added to 10 ml of trifluoroacetic acid and the mixture is cooled to 0°C. The methylene chloride solution is added slowly to the trifluoacetic acid solution and the mixture stirred for 30 minutes at 0°C. Excess borohydride is destroyed by the

dropwise addition of water (0.5 ml). Volatile components are removed under reduced pressure (roto-evaporator). Water is added to the residue (25 ml) followed by the addition of methylene chloride (25 ml). The methylene chloride layer is separated, washed twice with 25 ml of 5% aqueous sodium hydroxide and 25 ml of water. The methylene chloride solution is dried over sodium sulphate and then passed through a short (5 cm) basic alumina column. Evaporation of the solvent yields the product, m.p. 80-81°C, in >70% yield. (The m.p. of the hydrochloride salt is 119-121°C.)

EXAMPLE IV

Preparation of methoxy (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methane.

One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in 10 ml of THF. The solution is cooled to -78°C and lithium diisopropylamide in cyclohexane (1.1 mmole, 0.73 ml of a 1.5 M solution) is slowly added. Methyl iodide (1.2 mmole, 0.17 g) is added and the mixture permitted to warm to room temperature (30 minutes). The volatile components are removed under reduced pressure (roto-evaporator) and the residue is dissolved in methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulfate and is purified by passing the solution through silica gel column as in EXAMPLE I. The product, m.p. 96-98°C, is obtained upon evaporation of the solvent in a theoretical yield of >90%.

EXAMPLE V

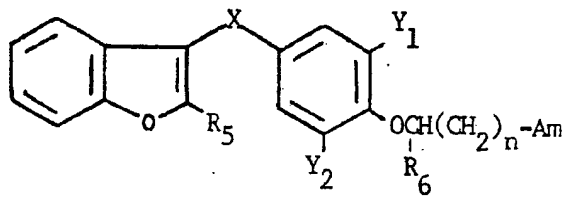
Preparation of (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methyl pivalate.

One mmole (647 mg) of the alcohol as prepared in EXAMPLE I is dissolved in pyridine (4 ml). Excess pivaloyl chloride (5 mmole, 605 mg) is added to the pyridine solution and the mixture heated to 65°C until the starting alcohol is completely consumed (approximately 12 hours). Volatile materials are removed under reduced pressure (roto-evaporator). The residue is dissolved in methylene chloride

and the methylene chloride solution washed twice with 25 ml of 5% aqueous sodium hydroxide and once with 25 ml of water. The methylene chloride solution is dried over sodium sulfate and then passed through a short (5 cm) basic alumina column. Evaporation of the solvent yields the product in >90% yield. (The m.p. of the hydrochloride salt is 108-110°C.)

THE CLAIMS:

1. A compound of the formula:



and pharmaceutically acceptable addition salts thereof wherein X represents a single, direct bond or a substituted or unsubstituted alkylene chain containing 1 to 4 carbon atoms wherein R_5 is a lower alkyl group, wherein R_6 is either hydrogen or methyl, wherein Am is a group selected from the class consisting of amino, lower mono and dialkylamino, piperidino, piperazino, N-lower alkyl piperazino, pyrrolidino, and morpholino groups, wherein Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen, halogen, methyl and ethyl and n is an integer in the range of 1-5.

2. A compound as set forth in Claim 1 wherein X represents an alkylene chain having the formula $-\overset{R_1}{\underset{R_2}{C}}-$ wherein R_1 and R_2 are each selected from the class consisting of hydrogen, a group having the formula $-OR_3$ with R_3 being a lower alkyl group, and a group having the formula $-O-\overset{O}{C}-R_4$ with R_4 being hydrogen or a lower alkyl group, R_4 is butyl, R_5 is hydrogen, Am is selected from the class consisting of amino and lower mono and dialkylamino and Y_1 and Y_2 are identical and are selected from the class consisting of

hydrogen, bromine, iodine, and methyl and n is an integer in the range of 1-3.

3. A compound as set forth in Claim 2 wherein R_2 is hydrogen and and R_1 is selected from the class consisting of hydrogen, a group having the formula $-OR_3$ with R_3 being a lower alkyl group, and a group having the formula $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl group, R_5 is butyl, R_6 is hydrogen, Am is selected from the class consisting of amino, ethylamino, and dialkylamino, Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen, iodine, and methyl and n is an integer in the range of 1-3.

4. A compound as set forth in Claim 2 wherein R_2 is hydrogen and R_1 is selected from the class consisting of hydrogen, $-OR_3$ with R_3 being a lower alkyl group containing between 1 and 4 carbon atoms, $-O-\overset{O}{\overset{\|}{C}}-R_4$ with R_4 being hydrogen or a lower alkyl containing 1-4 carbon atoms, R_5 is n-butyl, R_6 is hydrogen, Am is amino, ethylamino or diethylamino, Y_1 and Y_2 are identical and are selected from the class consisting of hydrogen, iodine, and methyl, and n is 1.

5. A compound as set forth in Claim 4 wherein both R_1 and R_2 are hydrogen.

6. A compound according to Claim 1 whereinsaid compound is 2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino) ethoxyl]-3,5 diiodophenyl] methane.

7. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-phenyl methane.

8. A compound according to Claim 1 wherein said compound is methoxy (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methane.

9. A compound according to Claim 1 wherein said compound is methoxy (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-phenyl methane.

10. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl methyl pivalate.

11. A compound according to Claim 1 wherein said compound is (2-n-butyl-3-benzofuranyl) 4-[2-(diethylamino)ethoxyl]-phenyl methyl pivalate.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03347

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07D 307/18; 405/10; 407/10

U.S.Cl.: 544/153,376; 546/196; 548/525; 549/469,471

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	544/153,376; 546/196; 548/525; 549/469,471

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	U.S , A, 3,248,401 (TONDEUR ET AL.) 26 April 1966. See the entire document.	1 & 2
Y	L. FIESER and M. FIESER "Advanced Organic Chemistry" published 1961, by Reinhold (New York), see pages 441-443 especially page 443.	1 & 2

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 DECEMBER 1988	10 FEB 1989
International Searching Authority	Signature of Authorized Officer
ISA/US	BERNARD DENTZ

Form PCT/ISA/210 (second sheet) (Rev.11-87)